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NEWS AND VIEWS

A theoretical model of mitotic spindle elongation under experimental constraints

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During the division of eukaryotic cells, the duplicated set of chromosomes is separated by the mitotic spindle, a large multicomponent assembly consisting of several hundred proteins in human cells (Sauer *et al*, 2005). Researchers have started to move from putting together the parts list of spindle components and from generating an atlas of their localizations toward trying to understand at a systems level the dynamic interplay between these components that ultimately translates into spindle function. This requires, in part, shifting the focus from biochemistry to mechanics. It is clear now that the mechanical properties of microtubules and molecular motors are crucial for spindle structure and function. But how they work together is still a mystery and there is a need for modeling this interplay, because our intuition reaches its limits when trying to understand it. The paper by Wollman *et al* (2008) in this issue reports on the next step of the development of a model that allows one to describe one aspect of spindle behavior for which good quantitative experimental data exist, namely spindle elongation during the period between prophase and anaphase B in *Drosophila* embryos. As their model is based on the mechanical properties of major elements of the spindle, the quantitative comparison with available data allows the authors to make predictions about how the concerted action of the different mechanical elements leads to spindle elongation.

Among others, there are two major challenges when trying to model the spindle (Karsenti *et al*, 2006). (1) What is the right level of description? This means what is the minimal set of molecular activities that needs to be considered and how much detail needs to be included in the model to have a chance of a rather close description of reality by the model? (2) What are the actual values of the parameters chosen to describe the properties of the molecular players considered in the model? In the ideal case, one would simply measure these parameter values experimentally and then use them for the model to see if it recapitulates the experimental measurement.

Wollman *et al* addressed these two challenges in the following manner. They chose a one-dimensional representation of the spindle as the basis of their model, as spindle elongation is essentially a one-dimensional problem. They assumed a pre-existing geometry of interconnected spindle components such as chromosomes, spindle poles, microtubules and motors that can vary in their exact configuration. They differentiated between different microtubule populations such as astral microtubules connecting the spindle poles to the cortex, microtubules connecting the spindle poles either to kinetochores or to chromosome arms and microtubules extending from opposite poles toward the spindle center where they overlap. Different motor populations localized to the cortex, kinetochores, chromosome arms or to the antiparallel microtubule overlap and regulated microtubule dynamics produce forces by acting selectively on one or the other microtubule population. The authors calculated the variation in spindle length from the sum of all forces produced by the different populations of the mechanical elements considered in their model. Variations in motor activity, microtubule dynamics or number of microtubules were represented by binary switches that change enzyme activity or microtubule number in a step-like manner during spindle elongation. In summary, the authors constructed a fully deterministic model for spindle elongation expressed as a system of ordinary differential equations with around 40 parameters.

Although the model contains strong simplifications, its total parameter value space is still enormous. Because it is not obvious how to solve the system of differential equations analytically, the full range of model behaviors cannot be grasped easily. Wollman *et al* therefore performed a massive screen of a very large range of parameter value combinations, an approach similar to a recent *in silico* screen of a pair of interacting microtubule asters (Nedelec, 2002). The system of differential equations for each parameter value combination was solved numerically and its output of spindle lengths was compared quantitatively with experimental data measured in *Drosophila* embryos, in spirit similar to an approach of another previous study where a theoretical model for kinetochore movements was quantitatively fit to experimental data of budding yeast spindles (Gardner *et al*, 2005).

The authors obtained a very large set of model variants that could reproduce spindle elongation in wild-type *Drosophila* embryos. Interestingly, and to a certain extent also expectedly, the number of model variants producing realistic behavior was significantly reduced when more experimental results from mutants were used as constraints (despite even an increase in the number of parameters in the model). Optimization strategies and cluster analysis boiled down the result to six distinct molecular scenarios potentially underlying spindle elongation, each scenario comprising several slightly different model variants perhaps reflecting a certain robustness of the scenarios. A major outcome was that certain features were shared between all identified scenarios suggesting core

characteristics of spindle functioning that are conserved. The analysis showed that outward forces originating from motors pushing on interpolar microtubules in the spindle center (in early prophase assisted also by forces of motors at the cortex pulling on astral microtubules) are largely balanced by inward kinetochore microtubule forces. Active microtubule depolymerization at the poles counteracted spindle elongation promoted by the outward-pushing motors in the spindle center. This depolymerization stops at the onset of anaphase B when the spindle elongates.

Although the number of possible scenarios could be gradually decreased considerably by successively adding more and more experimental constraints, this study has not yet identified the 'ultimate' scenario for *Drosophila* spindle elongation. It will be interesting to see if considering further experimental results in the future will narrow down the number of scenarios finally to one, representing the 'ultimate' model, or if it will drop even to below one, necessitating modification of the model. In the latter case, a critical evaluation of the assumptions inherent to the model would be required.

Despite the considerable number of model parameters, plausible, yet drastic simplifications had to be made to keep the model manageable. For example, a choice had to be made for the minimal set of essential spindle components required for the process under study. Furthermore, linear force–velocity relationships were used for entire populations of motors, although one expects theoretically that collective motor behavior is nonlinear (Klumpp and Lipowsky, 2005; Campas *et al*, 2006). Other examples for simplifications are the binary nature of the activity and number switches, simplified treatment of biochemical equilibria (no saturation) or the exclusion of the possibility of local concentration variations along the spindle axis. Finally, the deterministic nature of the model neglects any stochasticity that might be inherent to the real functioning of the spindle.

Continued development of modeling approaches such as the one chosen by Wollman *et al* and of alternative approaches with different degrees of coarse-graining as chosen by other researchers (Nedelec, 2002; Gardner *et al*, 2005; Goshima *et al*, 2005; Pecreaux *et al*, 2006; Schaffner and Jose, 2006; Burbank *et al*, 2007; Kozlowski *et al*, 2007) promises to move this field forward, especially if combined with experimental measurements of crucial parameter values identified by the modeling.

Two lines of experimental research will most likely be important in the future: gathering more quantitative information about the detailed dynamics of the key mechanical elements of the spindle as measured directly inside intact spindles. These experimental data will serve as a reference for the quantitative evaluation of the output produced by different models. Furthermore, it will be important to verify some of the key assumptions going into the modeling in well-defined systems by biochemical reconstitution approaches aiming at building more complex, functional subelements of the microtubule cytoskeleton from purified components *in vitro*. Such well-controlled *in vitro* systems have the charm of offering the possibility of having a rather complete knowledge of most of the parameter values relevant for the description of the system and provide therefore a rather direct test for the validity of the choice of simplifying assumptions going into the modeling (Surrey *et al*, 2001). Despite still some skepticism among some researchers regarding the feasibility of such engineering approaches, either in the test tube or in the computer, they have the potential for finally leading us to understand three-dimensional spindle morphogenesis and spindle function based on the physical properties of its components.

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